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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/889,812	12/04/2001	Mostafa Ronaghi	A34454-PCT-USA	8861

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EXAMINER	
CHAKRABARTI, ARUN K	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 08/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/889,812	Applicant(s) Ronaghi
	Examiner Arun Chakrabarti	Art Unit 1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jun 5, 2003* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-8, 10, and 15* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-8, 10, and 15* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action*

DETAILED ACTION

Status of the Application

1. The amendment received on June 9, 2003 has been entered. Claim 1 is newly amended and claims 9 and 11-14 have been canceled without prejudice towards further prosecution.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made

3. Claims 1-5 and 10 are rejected under 35 U.S.C. 103(a) over Studier et al. (U.S. Patent 5,547,843) (August 20, 1996).

Studier et al. teach a method of identifying a base at a target position in a sample nucleic acid (DNA) sequence wherein a primer, which hybridizes to the sample nucleic acid immediately adjacent to the target position, is provided and the sample nucleic acid primer are subjected to a polymerase reaction in the presence of a nucleotide whereby the nucleotide will only become incorporated if it is complementary to the base in target position, and the incorporation is detected , characterized in that, a single-stranded nucleic acid binding protein Eco SSB is included in the

polymerase reaction step (Abstract, Column 3, line 26 to column 6, line 21 and Figure 1 and Table 1).

Although Studier et al. teach the addition of the nucleic acid binding protein before the hybridization of the primer to the sample nucleic acid whereas in the claimed invention the order of addition of components have been reversed, it would have been prima facie obvious to switch the order of mixing ingredients to identify a base at a target position. MPEP 2144.04 further states, " *In re Gibson,* 39 F.2d 975, 5 USPQ 230 (CCPA 1930) Selection of any order of mixing ingredients is *prima facie* obvious".

4. Claims 6-7 are rejected under 35 U.S.C 103 (a) over Studier et al. (U.S. Patent 5,547,843) (August 20, 1996) in view of Nyren et al. (Analytical Biochemistry, (1985), Vol. 151, pages 504-509).

Studier et al teach the method of claims 1-5 and 10 as described above.

Studier et al do not teach the method, wherein the incorporation of the nucleotide is detected by monitoring the release of inorganic pyrophosphate.

Nyren et al. teach the method, wherein the incorporation of the nucleotide is detected by monitoring the release of inorganic pyrophosphate (Abstract, MATERIALS AND METHODS Section and RESULTS section).

Studier et al do not teach the method, wherein the release of inorganic pyrophosphate is detected using ATP sulphurylase and luciferase.

Nyren et al. teach the method, wherein the release of inorganic pyrophosphate is detected using ATP sulphurylase and luciferase (Abstract, MATERIALS AND METHODS Section and RESULTS section and Figures 1-8).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the method, wherein the release of inorganic pyrophosphate is detected using ATP sulphurylase and luciferase of Nyren et al. into the method of identifying a base at a target position in a sample nucleic acid of Studier et al., since Nyren et al. states, "The assay can be completed in less than 2s and is not affected by inorganic pyrophosphate. The method has been used for continuous monitoring of formation of Ppi in *Rhodospirillum rubrum* chromatophores. The assay is extremely sensitive, the linear range of the assay being 1X10 -5 to 10 -7 M Ppi. It is suitable for routine application. It is also possible to use the method for determination of low amounts of adenosine-5'-phosphosulfate (Abstract, lines 3-8)" By employing scientific reasoning, an ordinary artisan would have combined and substituted the method, wherein the release of inorganic pyrophosphate is detected using ATP sulphurylase and luciferase of Nyren et al. into the method of identifying a base at a target position in a sample nucleic acid of Studier et al., in order to improve the assay system. An ordinary practitioner would have been motivated to combine and substitute the method, wherein the release of inorganic pyrophosphate is detected using ATP sulphurylase and luciferase of Nyren et al. into the method of identifying a base at a target position in a sample nucleic acid of Studier et al., in order to achieve the express advantages, as noted by Nyren et al., of a novel process that is extremely

sensitive, the linear range of the assay being 1X10 -5 to 10 -7 M Ppi and suitable for routine application and which enables the determination of low amounts of adenosine and hence marked reduction of the operation time as compared with conventional processes.

5. Claim 8 is rejected under 35 U.S.C 103 (a) over Studier et al. (U.S. Patent 5,547,843) (August 20, 1996) in view of Shultz et al. (U.S. Patent 6,335,162 B1) (January 1, 2001).

Studier et al teach the method of claims 1-5 and 10 as described above.

Studier et al do not teach the method, wherein apyrase is present during the polymerase reaction.

Shultz et al. teach the method, wherein apyrase is present during the polymerase reaction (Column 14, lines 47-67 and Column 16, lines 28-59).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the method, wherein apyrase is present during the polymerase reaction of Shultz et al. into the method of identifying a base at a target position in a sample nucleic acid of Studier et al., since Shultz et al. states, "The reaction must be fed AMP, preferably Apyrase treated AMP so that background due to contaminating ADP and ATP is minimized (Column 14, lines 55-57)" An ordinary practitioner would have been motivated to combine and substitute the method, wherein apyrase is present during the polymerase reaction of Shultz et al. into the method of identifying a base at a target position in a sample nucleic acid of Studier et al., in order to achieve the express advantages, as noted by Shultz et al., of apyrase in the reaction mixture which minimizes the background due to contaminating ADP and ATP.

6. Claim 15 is rejected under 35 U.S.C 103 (a) over Studier et al. (U.S. Patent 5,547,843) (August 20, 1996) in view of Stratagene Catalog (1988, Page 39).

Studier et al. expressly teach the method claims 1-5 and 10 as described above in detail.

Studier et al. et al do not teach the motivation to combine all the reagents including Eco SSB for sequencing by amplification of a nucleic acid in the form of a kit.

Stratagene catalog teaches a motivation to combine reagents into kit format (page 39).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine a suitable container and all the reagents including Eco SSB for sequencing by amplification of a nucleic acid of Studier et al, into a kit format as discussed by Stratagene catalog since the Stratagene catalog teaches a motivation for combining reagents of use in an assay into a kit, "Each kit provides two services: 1) a variety of different reagents have been assembled and pre-mixed specifically for a defined set of experiments. Thus one need not purchase gram quantities of 10 different reagents, each of which is needed in only microgram amounts, when beginning a series of experiments. When one considers all of the unused chemicals that typically accumulate in weighing rooms, desiccators, and freezers, one quickly realizes that it is actually far more expensive for a small number of users to prepare most buffer solutions from the basic reagents. Stratagene provides only the quantities you will actually need, premixed and tested. In actuality, the kit format saves money and resources for everyone by dramatically reducing waste. 2) The other service provided in a kit is quality control". (page 39, column 1).

Response to Amendment

7. In response to amendment, 112 (second paragraph) rejection, 102(b) rejection and previous 103 (a) rejection with respect to claims 12-14 have been withdrawn. However, three new 103(a) rejections have been included.

Response to Arguments

8. In response to applicant's arguments, objection against claims 5-10 has been withdrawn. Applicant's argument (Page 5, last paragraph to Page 6, first paragraph) to withdraw 103(a) rejection with respect to kit claim 15 has been considered but it is not persuasive. Applicant argues that Studier et al reference does not teach a method of sequencing-by-synthesis. In response to applicant's argument that the cited refrence teaches a different method of primer walking using the same chemicals (nucleotides, a polymerase, means for detection of incorporation and single stranded nucleic acid binding protein) having same structures and functions, a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

Moreover, applicant's arguments with respect to other claims have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CAR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CAR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti, Ph.D., whose telephone number is (703) 306-5818. The examiner can normally be reached on 7:00 AM-4:30 PM from Monday to Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703) 308-1119. The fax phone number for this

Group is (703) 305-7401. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group analyst Chantae Dessau whose telephone number is (703) 605-1237.

Arun Chakrabarti,

Patent Examiner,

August 13, 2003

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